IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	Art Unit: 1615
Gilbert J. GRANT et al	)	Examiner: K. Gollamudi
Appln. No.: 10/620,006	)	Washington, D.C.
Date Filed: July 16, 2003	)	Confirmation No. 7468
For: LIPOSOMAK COMPOSITIONS AND METHODS OF PREPARATION	)	ATTY.'S DOCKET: GRANT=1A

DECLARATION UNDER 37 CFR 1.132

Honorable Commissioner for Patents
U.S. Patent and Trademark Office
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Sir:

I, Yechezkel Barenholz, do hereby declare that I am one of the inventors of the above-identified application.

Experiments were conducted under my direction and control to demonstrate that it is critical when preparing liposomes according to the present invention that the liposomes be washed with hyperosmotic saline in order to reduce the liposome size and provide a higher than expected concentration of bupivacaine.

Liposomes produced by the dehydration-rehydration (DRV) technique loaded with bupivacaine were prepared and

washed with normal saline solution. The liposomes so washed had 12.90 mg bupivacaine/ml (36.0 nmol·phospholipid (PL)/ml).

The same liposomes when washed with normal saline followed by a final wash with a hyperosmotic saline, resulted in 25.9 mg bupivacaine/ml (95.5 nmol PL/ml).

The final wash of the bupivacaine-loaded liposomes partially dehydrated the liposomes, resulting in reduced liposomal size and intraliposome aqueous phase, and therefore a higher liposome pellet concentration, and an almost two-fold higher concentration of bupivicaine.

In addition, the formation of the liposomes under conditions in which the drug is at a supercritical concentration, as in the present invention, followed by partial dehydration of the liposomes with a hyperosmotic saline, resulted in the precipitation/gelation of the drug within the liposomes and thereby reduced leakage of the drug from the liposomes.

The results described above clearly demonstrate that a higher concentration of bupivacaine is obtained when performing an additional wash of the liposomes with hyperosmotic saline.

I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and

further that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 81 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

By Yechezkel Barenholz
Yechezkel BARENHOLZ

Date: 24. August. 2004

DoctorSpiller.Com

Local Anesthetics

- The history of Local anesthetics
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  - Lidocaine
  - Prilocaine and Mepivicaine
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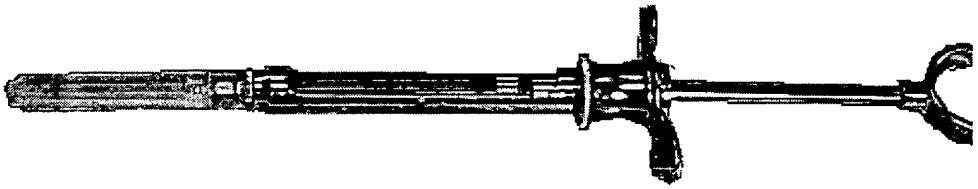
  - Nervousness and fast heart beat directly after shot
- What if you are **allergic** to local anesthetics?
- Can local anesthetics cause **false positive drug tests**?
  - Drug testing: Your rights versus the employer

Gum Disease
Treatment of Perio
Prevention
Partial Dentures
Root Canals
Post and Core
Extractions
TMJ
Orthodontics
Crowns
Dental Implants
Snore Guards
Deprogrammer
Fluoride
Cracked Teeth
Aids
Dental Materials
Oral Anatomy

It is estimated that the average dentist administers between 15C 2000 injections of local anesthesia each year. By definition, ther every dentist is an expert in the field of local anesthesia, which is extremely good thing, since without the ability to produce profou numbness, modern dentistry would be all but impossible.



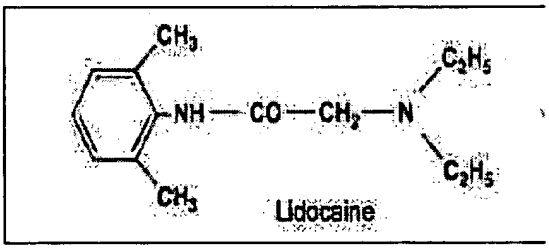
The history of local anesthetic agents.

Surprisingly, the first local anesthetic was Cocaine which was iso from coca leaves by Albert Niemann in Germany in the 1860s. Tl first clinical use of Cocaine was in 1884 by (of all people) Sigmur who used it to wean a patient from morphine addiction. It was F his colleague Karl Kollar who first noticed its anesthetic effect. K introduced it to clinical ophthalmology as a topical ocular anesthe in 1884, Dr. William Stewart Halsted was the first to describe the of cocaine into a sensory nerve trunk to create surgical anesthes Halsted was an eminent surgeon who had been trained in Britain the first to establish formal surgical training for physicians in Am Prior to that time, surgery was a self taught discipline among US physicians. He also invented and pioneered the use of rubber glo Unfortunately, much to his own regret, he began to use cocaine l and became highly addicted to it. At that time, there was no stig attached to the recreational use of cocaine, and it gained a follow among the elites of the day. Arthur Conan Doyle's Sherlock Holr supposed to be an addict, and Holmes kept Dr Watson around as for his drugs, as well as for the comic relief he provided.

It became fairly obvious fairly quickly that while the anesthetic characteristics of cocaine were desirable, the euphoria and subse addiction it produced was not! The turn of the century was a tre time of scientific progress, and the new discipline of organic cher enabled the synthesis of the first analog of cocaine in 1905. (An of a chemical molecule is one in which the original molecule is

progressively modified to retain and enhance certain holistic characteristics of the original substance while ridding it of other u characteristics.) The first synthetic local anesthetic was **procain** remembered today by its trade name, "**Novocain**".

Novocain was not without its problems. It took a very long time (ie. to produce the desired anesthetic result), wore off too quickl was not nearly as potent as cocaine. On top of that, it is classifie ester. Esters tend to have a very high potential to cause allergic reactions. It is estimated that about one third of all persons wh received it developed at least minor allergic reactions to it. Face the legal and ethical difficulties associated with the use of cocain local anesthetic, and with the inefficiencies and allergenicity asso with the use of procaine, it is not surprising that most dentists of worked without any local anesthetic at all. (Nitrous oxide gas wa available during this period.) Today, procaine is not even availat dental procedures.

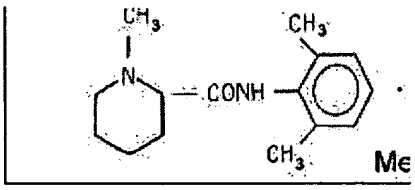


Lidocaine

The first modern local anesthetic agent was **lidocaine** (trade name **Xylocaine®**). It was invented in the 1940s. Prior to its introduction, Nitrous oxide gas (plus alcohol in the form of whiskey) was the major source of pai during dental procedures. Lidocaine proved to be so successful t during the 1940s and 1950s the use of Nitrous oxide gas as a pri anesthetic agent all but vanished. (Whiskey somehow survived, no longer used on patients.) Today, nitrous oxide is used princip an anti-anxiety palliative. Lidocaine is in a broad class of chemic amides, and unlike ester based anesthetics, amides tend to be hypoallergenic. It sets quickly and when combined with a small a of **epinephrine (adrenalin)**, it produces profound anesthesia fc hours. Lidocaine is still the most widely used local anesthetic in today.

Over the next thirty years, a number of other amide local anesth were invented, most not differing significantly from lidocaine. Th problem with lidocaine and its analogs is that they cause **vasodil** the tendency of the local blood vessels to open wider increasing flow in the area. This causes the anesthetic to be absorbed too c take effect. Hence these anesthetics are always mixed with low concentrations of epinephrine which has the opposite effect (ie **vasoconstriction**) and closes the blood vessels down to keep th anesthesia in position long enough to produce long lasting numb

Mepivicaine (Carbocaine®) and



prilocaine (Citanest®) have much less vasodilative qualities and hence can be used without the epinephrine vasoconstrictor. The advantage to this is that these anesthetics can be used more safely in patients who are taking medications which may in negatively with the vasoconstrictor. These drugs include certain pressure medications (most notably beta blockers and MAO inhib tricyclic antidepressants (Elevil® and imipramine are two examp thyroid replacement hormones (Synthroid®).

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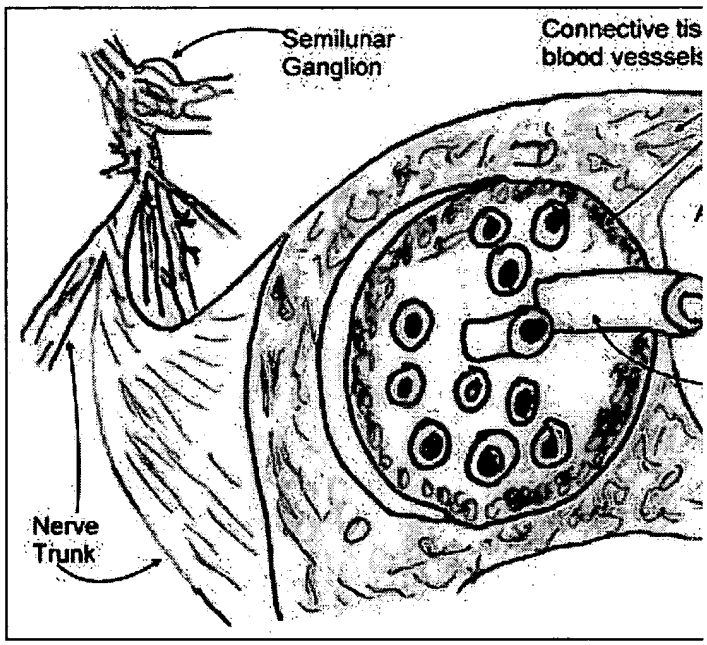
How nerves conduct an impulse



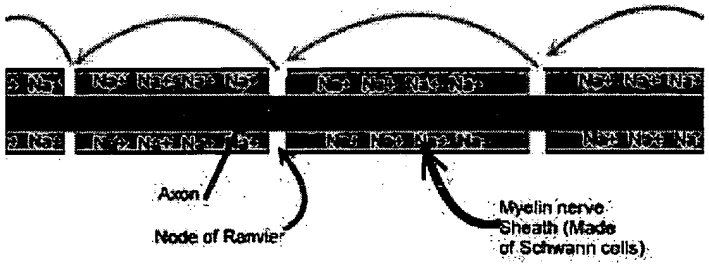
The image to the right is a fairly accurate representation of a nerve bundle. (For a detailed explanation of this diagram as well as nerve anatomy and physiology, see my page on Understanding Pain.) If you think of a nerve bundle as an electrical cable, the blue axons represent the "wires" that carry the impulse from the tooth to the ganglion at t end. The rest of the tissue surrounding the axons represent the "insulation" which separates the various wires in the cable from other. At this point, the analogy breaks down because, while th insulation in an electrical cable is a passive material that serves separate the wires from each other to prevent short circuits, the insulation in a nerve bundle is an active participant in the condu the impulse.

The connective tissue that is associated with each neuron is com a special material called **myelin** which is itself made up of the ce of specialized cells called **Schwann cells**.

The myelin sheath is almost continuous along the entire axon. T are, however tiny breaks in the continuity of the myelin sheath each succeeding Schwann cell. These breaks are called "**nodes**

Ranvier". These nodes are quite important in the conduction of impulse along a nerve axon on its way to the cell body in the gai mostly because their presence along the way speeds the impulse bit.

How a nerve fiber transmits an impulse



Nerves are NOT like electrical wires with electrons traveling their to transfer information from one end to the other. They are actu complex electro-chemical structures which utilize the electrical p difference between the fluid inside of the axon, and the fluid that surrounds the axon. The fluid inside the axon (called cytoplasm) a high concentration of potassium ions, while the fluid outside co high concentration of sodium ions. There is no real difference in potential between a potassium ion and a sodium ion, however, tl that they exist in different concentrations on either side of the ce membrane sets up an electrochemical pressure gradient betweer two. Sodium ions want to flow into the nerve cytoplasm, while tl potassium ions want to flow out, but both are prevented from do the presence of the nerve cell membrane.

When a nerve is stimulated, this sets up a chain reaction in which sodium ions begin to penetrate through the nerve cell membrane and flow into the axon, while potassium ions begin to flow out. This activity happens at the nodes of Ranvier. This process is called **depolarization** of the nerve membrane. The imbalance in the chemical makeup of the extracellular fluid then causes an imbalance in the concentration of sodium ions at the adjacent node which stimulates an identical depolarization at this node as well. This process proceeds from node to node until the impulse reaches the cell body of the nerve in the ganglion where it stimulates a similar cascade in a network of other neurons which make contact with it.

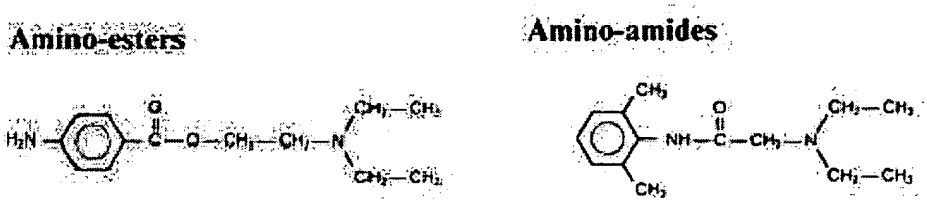
You might think that once all the potassium and sodium ions have exchanged places, the nerve would no longer be able

to conduct impulses. The nerve, however, is a living entity and can regenerate the original concentrations of ions using energy from the food you eat in almost the same way that muscle cells use that same energy to cause muscle movement. It does this using proteins embedded in the cell membrane which act as "ion pumps".

How local anesthesia interrupts this process

Local anesthetics work to block nerve conduction by reducing the influx of sodium ions into the nerve cytoplasm. If the sodium ions cannot flow into the neuron, then the potassium ions cannot flow out, thus inhibiting the depolarizatior nerve. If this process can be inhibited for just a few nodes of Ra along the way, then nerve impulses generated downstream from blocked nodes cannot propagate to the ganglion. **In order to accomplish this feat, the anesthetic molecules must actua through the cell membrane of the nerve. Herein lies the differences in the potency, time of onset and duration of t various local anesthetics.**

The structure of local anesthetics

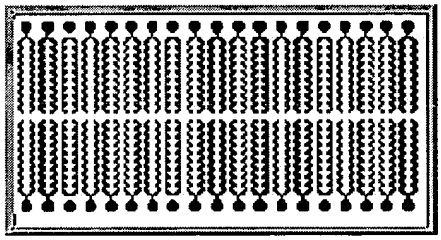


The diagrams above show the essential structures of the two ma of local anesthetic agent; the molecule shown in the left diagram represents the structure of procaine (Novocain). The chain that the benzene ring on the left with the amide tail on the right is an linkage". The diagram to the right represents lidocaine and its a The connecting chain in this case is called an "amide linkage". T linkage contains an extra nitrogen to the left of the C=O (carbox group.

All local anesthetics are weak bases. They all contain: 1. an aror group (the benzene ring seen on the left side of both structures 2. an intermediate chain, either an ester or an amide; and 3. an group seen on the right side of both molecular structures above. characteristics of any given anesthetic is determined by the exac structure and relationship of each of these three components. Tl aromatic ring structure is soluble in lipids (The nerve cell membr made of a lipid bilayer and thus the aromatic ring is important in it possible for the anesthetic molecule to penetrate through the r

membrane. The amino structure (seen on the right side of the m diagramed above) is soluble in water which is what makes it pos the anesthetic molecule to dissolve in the water in which it is deli from the dentist's syringe into the patient's tissue. It is also resp for allowing it to remain in solution on either side of the nerve membrane. The trick that the anesthetic molecule must play is c from one side of the membrane to the other.

The structure of the cell membrane



Every cell in the body has a membrane which separates that cell other cells, and from the extracellular fluids that surround it. Th membrane has a definite chemical structure which creates a stab dimensional sheet which naturally retains its structure in aqueou based) solution. It is composed of a bilayer of phospholipid mole arranged as shown in the diagram above. Each phospholipid mo composed of two components; a phosphate radical (shown as a l which tends to carry an electrical charge, and therefore likes to a with water molecules, and two long hydrocarbon chains (green) not carry a charge and therefore tend to associate with each oth order to avoid contact with the surrounding water molecules. (Nc oil, which does not mix with water either). The stability of this st is based on the fact that the phosphate radicals face outward int surrounding medium. They are soluble in water and mix well wi the other hand, the lipid tails are hydrophobic and avoid contact water relying on the phosphate radicals to "protect" them. The l mingle with each other in the same way that the pioneers used t the wagons" in order to protect themselves. This maintains the integrity of the membrane. This super stable micro structure is p one of the most important chemical structures in all of creation b enables the formation of discreet biological elements separated i cellular components.

While the phospholipid bilayer defines an essentially two dimensi sheet, it actually has a third dimension meaning that it has thick addition, the bilayer is essentially a non aqueous liquid, and as s other structures such as proteins can be embedded within it, floa around in this miniature ocean of phospholipids. The proteins ca complex shapes and functions depending upon the structure pro

for them by the genetic machinery of the cell. It is thought that channels that the allow the influx of sodium ions, as well as the e potassium ions during depolarization of the membrane are actua complex protein structures embedded in the neuron membrane.

The phospholipid bilayer not only exists as a chem entity. It can actually be seen on electron microg The thumbnail on the left shows HIV virons buddir natural human T cell . The lipid bilayer is clearly v both the mother cell and in the budding virons. C the thumbnail to view the image at full resolution.

PH, PKa, Acids and Bases---and why they are the k the effectiveness and longevity of an injectable loc anesthetic

This section is quite conceptually difficult because it involves some essential chemistry, but it makes for very rewarding reading because it will enable the reader to understand the differences between the common local anesthetic solutions. It will help to explain the reasons that some anesthetics take longer to set than others, and why some cause more prolonged anesthesia than others.

Synthetic anesthetics are prepared as weak bases and during manufacture, precipitate as powdered solids. These solids are poorly soluble in water. They are therefore combined with an acid to form a salt which can be combined with sterile water or saline. The salt dissolves to produce a stable solution which is injectable. The PH (the acid/base balance) of the solution is adjusted to complement the specific molecular structure of the anesthesia in question. Remember that the lower the PH, the more acidic the solution is, and the higher the PH, the more alkaline (basic) it is.

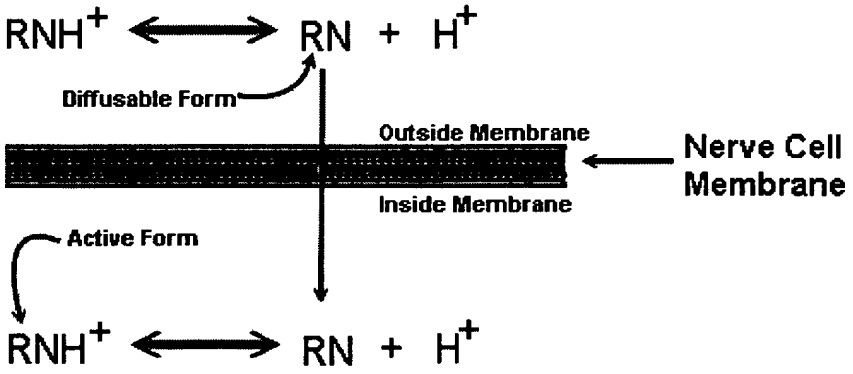
In any given solution of anesthetic, the molecular structure shifts between two forms; an uncharged base molecule (RN) and a positively charged cation (RNH+). ("R" stands for the chemical term "radical" and is the symbol for the generic molecular structure, whether it carries a charge or not.) These two forms of the anesthetic molecule exist in an

equilibrium dependent upon the exact PH of the solution:

$$RNH^+ \longleftrightarrow RN + H^+$$

As the solution becomes more acidic (lower PH), the concentratic hydrogen ions increases. These positively charged ions combine uncharged anesthetic radical (molecule) shifting the above equat the left, and producing a higher proportion of charged cationic st As the PH rises, (ie. the solution becomes more alkaline) there a positively charged hydrogen ions. Thus the charged radicals ten release their hydrogen ions into solution and the equation shifts right producing more of the uncharged base.

The PH that produces an **equal** number of uncharged basic mole (RN) and charged cationic forms (RNH+) is called the **PKa**. This important because **the molecular form of the anesthetic that to diffuse through the lipid membrane of the nerve cell is t uncharged (RN) form, while once inside the neuron, the a form that inhibits sodium influx is the charged cationic (R form**. As more and more of the uncharged base diffuses throug membrane, the concentration of the uncharged base outside the membrane goes down and the formula re-equilibrates forming m the uncharged base from the newly higher concentration of posit cations. This continues until all the base eventually diffuses from outside of the cell membrane to the inside. Once inside the cell membrane, the formula shifts to the left recreating the original concentrations of positive and negatively charged base molecule:



The PH of normal body tissue is 7.4. In situations in which there active infection present, the tissue PH can be considerably lower, vicinity of 5 or 6. This very reduced PH shifts the equation (outs nerve cell) to the left reducing the number of neutral (RN) radica available to diffuse through the nerve cell membrane. This accou the difficulty in anesthetizing such an area. The relative differen

between the PKa of the anesthetic and the PH of the body tissue make quite a large difference in the percentage of anesthetic tha available to diffuse immediately through the nerve membrane, a on the amount of time it takes for the anesthetic effect to be felt table below shows the PKa and other vital statistics of the seven commonly used dental anesthetics:

Anesthetic	PKa	% RN at PH 7.4	Onset in r
Mepivicaine	7.6	40	2 to
Etidocaine	7.7	33	2 to
Articaine	7.8	29	2 to
Lidocaine	7.9	25	2 to
Prilocaine	7.9	25	2 to
Bupivicaine	8.1	18	5 to
Procaine	9.1	2	14 to

When an anesthetic solution is injected into healthy tissue, it eve takes on the PH of the surrounding tissue which is 7.4. This is w third column labeled "% RN at PH 7.4" is important. Remember the uncharged basic RN radical can penetrate the lipid membran components. The higher this percentage is, the **quicker** the ane penetrates the membrane.

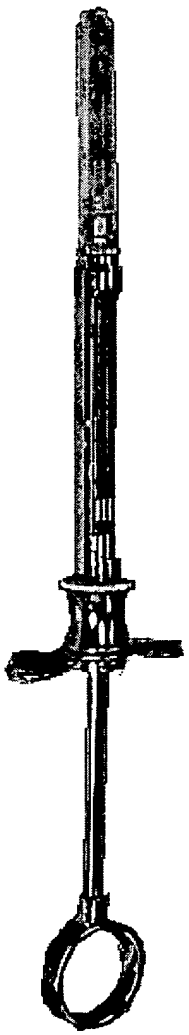
Just because only, say, 18% of an anesthetic solution is available diffuse through the cell membrane at any one time, this does not that all the anesthetic molecules cannot eventually diffuse into th cells. As the number of RN radicals decreases outside of the ner because of absorption, more of the cationic form (RNH+) conver RN form to maintain the dynamic balance between the two form tissue PH simply delays the process. Unfortunately, as the time increases, the chances of the unused anesthetic being absorbed blood stream also increases, which is why procaine was abandon soon as lidocaine became available. It simply "wore off" before i chance to enter the nerve and take effect.

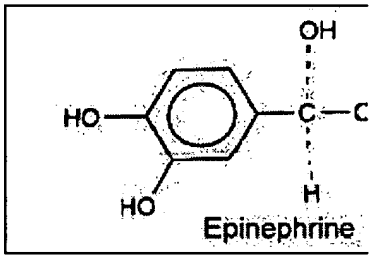
Once the molecules diffuse through the membrane, the neutral b is once again subject to the PH dependent equation above, and r neutral RN radicals shift back to their cationic form (RNH+) to m the dynamic balance inside the neuron. **Once inside the nerve the active component that combines with the sodium ion is the acidic cation form (RNH+).**

The irony of this situation is that now the slowest diffusing anest

(Bupivicaine with only 18% available to diffuse through the mem has the distinct advantage of being the **MOST long lasting** anes available, with 82% (100% minus 18%) of the absorbed radicals binding with the sodium channel proteins to block their activity! doesn't count since it takes so long to diffuse through the nerve membrane that most of it has been reabsorbed by the blood ves: before it ever has a chance to penetrate the nerve membrane.) Bupivicaine (Marcaine®) is used today for prolonged surgical ope as a way of maintaining numbness for many hours after the proc help reduce postoperative pain.

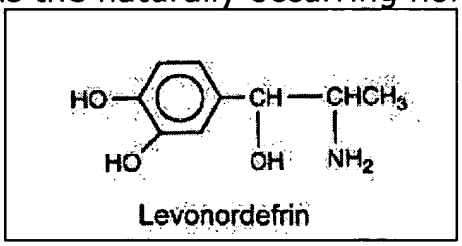
Vasoconstrictors





Epinephrine

No matter how quickly an anesthetic agent can enter a nerve, the local blood vessels begin to absorb the unused anesthetic as soon as it is injected. In order to slow this process down, manufacturers of these solutions add a substance tl concentrations acts to cause the local blood vessels constrict, or narrow down. This restricts the amour blood and plasma entering and leaving the site of tl injection which has the net effect of slowing the vas absorption of the anesthetic solution. This keeps th anesthetic solution in place longer and prolongs the the drug. The substance used to do this is called a **vasoconstrictor** (vaso refers to blood vessels and constriction means to close down). The vasoconstri is the naturally occurring hormone **epinephrine** or



Levonordefrin

analogs called **levonordefrine**. Epin is an ideal vasoconstric because it is manufacti naturally by the body a **adrenaline**, sometime the "fight or flight horn In addition to causing a constriction of blood supply enters the general circulation it can cause an increa rate and stronger heart beat, along with a feeling o nervousness. These side effects account for the "rush" that som feel after receiving an anesthetic shot.

The downside to vasoconstrictors

All anesthetic solutions are sold with added vasoconstrictor. Onl

mepivicaine and **prilocaine** are sold with or without vasoconsti
Mepivicaine and prilocaine have the advantage of producing only
vasodilation and, though both are short acting without their
vasoconstrictor added, they still produce adequate anesthesia fo
procedures. The major advantage of using an anesthetic withou
vasoconstrictor is that there are virtually no interactions with oth
the patient may be taking. Vasoconstrictors may not be used wi
types of blood pressure medications, artificial thyroid hormones,
tricyclic antidepressants.

Vasoconstrictors are also not used in any body area in which the
supply must "double back" on itself. This includes such blind end
appendages as the tip of the nose, or the fingers or toes. In the
a vasoconstrictor may block all blood flow to the appendage cau
tissue necrosis (death of the tissue).

The use of vasoconstrictor does carry one additional penalty for t
practitioner. These naturally occurring hormones are not very st
must be stabilized by the addition of an acidic preservative. The
of the preservative can lower the PH of the anesthetic solution tc
range of 3.8 to 5.0, thus reducing the amount of the neutral basi
(RN) and slowing the onset of action of the anesthetic. This effe
thankfully not especially significant, and anesthesia with vasocon
far and away the most popular choice among practitioners when
clinical considerations permit its use.

Toxicity; How much is too much?

The maximum dose for local anesthetic solutions is somewhere b
70 mg to 500 mg. Of course, the miximum dose is dependent u
age and health of the patient, the type of solution used, and whe
vasoconstrictor is present or not. These anesthetic agents are di
in concentrations that are appropriate to their toxicity and their
anesthesia producing qualities. All dental anesthetics that are di
with vasoconstrictor (with the exception of bupivicaine, prilocaine
articaine which will be covered later) come in 2% concentrations
Mepivicaine without vasoconstrictor is distributed in 3% concent
The carpules (cartridges) that these drugs are distributed in cont
ml of solution (Articaine carpules contain 1.7 ml).

Since people vary in age, weight and health, the maximum dose
given drug that any individual can tolerate varies widely and can
computed arithmetically. The maximum dose (for a normal adul
pounds and up) for Articaine and lidocaine is 500 mgm. The ma
dose of mepivicaine and etidocaine is 400 mgm. The maximum
prilocaine is 600 mgm, and the maximum dose of bupivicaine is
A 2% solution contains 20 mg of anesthetic agent per milliliter w

means that each 1.8 ml cartridge contains 36 mg of agent. In th lidocaine, this works out to about 13 carpules delivered at one tir children, it works out to about 1/3 to 1/2 that number dependinç weight. These doses are **not** considered lethal. They are simply doses at which **some** people **begin** to feel toxic systemic effects drugs which may include CNS (Central Nervous System) effects (sedation, light headedness, slurred speech, shivering or twitchinç rare cases, seizures; or cardiovascular effects such as hypotensic blood pressure). The incidence of toxicity to local anesthetics in dental setting is extremely rare and generally revolve around vei unusual patient centered physiologic abnormalities rather than p anesthetic technique on the part of the dentist. The most freque related toxic effect in the dental setting is nervousness and high rate, due not to the effect of the anesthetic itself, but rather to tl systemic effect of the vasoconstrictor.

Three special cases

Bupivicaine (Marcaine®)

Bupivicaine is a special case in dental anesthesia. It is used mos surgeons who want to produce very long acting anesthetic effect to delay the post operative pain from their surgery for as long as possible. Bupivicaine comes in 0.5% solution with a vasoconstric the most toxic of all the anesthetic agents and this toxicity is refl its low concentration in the carpules. As noted in the PKa table a is has a very alkaline (basic) PKa which means that a relatively lc percentage of the uncharged base radical (RN) is available for im diffusion through the cell membrane. Thus it takes a fairly long t set. However, once inside the cell membrane, over 80% of the r that do diffuse become available for binding to the sodium chann proteins. This high protein binding ability causes the drug to ren active for a long time once it has diffused through the cell memb

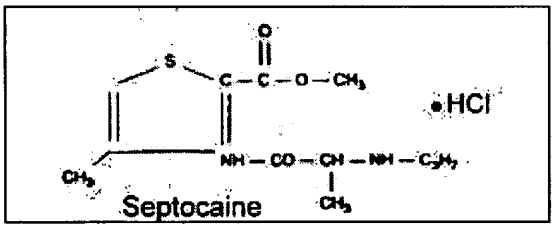
Prilocaine (Citanest®)

Prilocaine has the same general PKa as lidocaine, which means that for all practical purposes it can be used in the same way and at the same concentrations as lidocaine, producing about the same anesthetic affect in the same

setting time for the same duration. It is, however somewhat less toxic in higher doses than lidocaine, and thus is delivered in a 4% solution which places about twice as much molecular anesthetic in proximity to the nerve as is the case with lidocaine or mepivicaine. In addition, since it has little vasodilatory activity, it may be used without a vasoconstrictor. The higher concentration of anesthetic agent, in combination with a vasoconstrictor, therefore, gives this anesthetic the twin advantages of fast onset of activity with prolonged anesthetic activity due to the larger number of molecules available to cross the cell membrane. Unfortunately, the toxicity of a single carpule of 4% prilocaine is still greater than the toxicity of a single carpule of 2% lidocaine which means that fewer carpules can be used before toxic levels are reached.

Articaine (Septocaine®)

Articaine is the newest addition to the local anesthetic arsenal and was approved by the Food and Drug Administration in April 2000. It has been in use in Europe since 1976 and in Canada since 1983. Its approval in the US has been delayed by the FDA due to the presence of a preservati the agency said was unnecessary in single use carpules and was potential allergen. It was approved when the French company Se finally removed the preservative from American shipments.



Articaine has the same PKa an as Lidocaine, however it is me differently. It has a half life in body less than 1/4 as long as lidocaine and only 1/5 as long mepivicaine. This means that the drug can be injected later in the dental procedure will less lik of blood concentrations building to toxic levels. Articaine is formu a 4.0% solution with vasoconstrictor. The presence of the vasoc retards the systemic absorption of the anesthetic allowing higher concentrations of the drug to remain in the area of injection and the absorption into the bloodstream. The higher local concentrat the drug produces a high level of the uncharged radical (RN) to b present at the membrane which brings about very rapid absorpti drug. In addition, the benzene ring on the left end of the molecu been replaced with a thiophene ring. This modification allows for and more complete absorption through the nerve cell membrane ability of this drug to penetrate barriers is so great that it has be to penetrate thick bone to produce anesthesia in a way that othe anesthetics cannot. Articaine has become the local anesthetic of